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to

The National Toxicology Program

- Appendix 5 -

**A Probabilistic Risk Analysis of
Lung Cancer Mortality
Associated with ETS Exposure**

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Introduction

For the purpose of demonstrating the fragility of the United States Environmental Protection Agency's (U.S. EPA) attributable death calculations in its Risk Assessment on ETS (1992), we utilized U.S. EPA's relative risk point estimate. It is important to note that we do not believe that this point estimate is scientifically justified. In fact, the data indicate that one cannot distinguish the association between reported exposure to ETS and lung cancer described by the EPA from no association.

The statistical analysis provided by Philip Morris in this section examines the influence of just two of several possible modifications to some of the assumptions employed by the U.S. EPA in its Risk Assessment on ETS (1992). The technique of Monte Carlo simulation is used to construct a probabilistic model of estimated mortality purportedly associated with ETS exposure; it emphasizes the uncertainty associated with the single estimate reported by the U.S. EPA. The reduction in the number of so-called attributable deaths that follows from changes in only two factors reinforces our position that the U.S. EPA failed to utilize reasonable statistical assumptions in its estimation of the number of attributable deaths in its report.

A Probabilistic Risk Analysis of Lung Cancer Mortality Associated with ETS Exposure

The U.S. EPA's (1992) estimates of female and male annual lung cancer mortality in nonsmokers (never smokers plus former smokers who have quit for 5+ years) purportedly

attributable to ETS sources for the United States are shown in Table 1. EPA's total estimate of 3,060 deaths among nonsmokers attributable to ETS exposure has two main components: (i) 2,200 deaths attributed to "Background" (non-spousal) exposure to ETS, primarily in the workplace and other away-from-home settings, and (ii) 860 deaths attributed to "Spousal" exposure to ETS from a spouse who smokes.

The estimated mortality associated with Background and Spousal ETS exposure is a function of two key parameters: (i) the Relative Risk (RR) of lung cancer for nonsmokers exposed to spousal ETS relative to nonsmokers not exposed to spousal ETS (but who are exposed to background ETS), and (ii) the Z-factor, which is the ratio between the mean dose level in the "exposed" (spousal ETS) group and the mean dose level in the "unexposed" (non-spousal or background ETS) group. The value of Relative Risk assumed by the EPA is $RR = 1.19$ (90% CI: 1.04-1.35), based on EPA's meta-analysis of 11 U.S. epidemiological studies of never-smoking females. The RRs from the 11 studies were corrected for smoker misclassification prior to the meta-analysis using a 1.09% misclassification rate. However, the RRs were not corrected for other likely sources of bias, such as confounding due to dietary and other lifestyle factors inherent in the spousal smoking design, as well as recall bias. The value of the Z-factor assumed by EPA is $Z = 1.75$, and is based on U.S. urinary cotinine studies cited by EPA.

As stated in EPA's report *Respiratory Health Effects of Passive Smoking* (EPA, 1992), the estimated mortality attributed to Background ETS exposure is proportional to $(RR - 1) / (Z - RR)$, and can be computed as

Table 1. U.S. EPA's estimates of annual lung cancer mortality.

Estimated annual lung cancer mortality						
Smoking status	Sex	Exposed to spousal ETS	Population (in millions)	Background ETS	Spousal ETS	Total ETS
Never-Smoker	F	No	12.92	410		410
Never-Smoker	F	Yes	19.38	620	470	1090
Never-Smoker	M	No	9.93	320		320
Never-Smoker	M	Yes	3.13	100	80	180
Former Smoker	F	No	2.0	60		60
Former Smoker	F	Yes	6.7	210	160	370
Former Smoker	M	No	8.8	280		280
Former Smoker	M	Yes	6.2	200	150	350
TOTAL			69.07	2200 (71.9%)	860 (28.1%)	3060

$$\text{Estimated Mortality Attributed to Background ETS} = 6484.21 \times \frac{RR - 1}{Z - RR}$$

where 6484.21 is a proportionality constant such that EPA's estimate of 2,200 is obtained when $RR = 1.19$ and $Z = 1.75$. Similarly, the estimated mortality attributed to Spousal ETS exposure is proportional to $(RR - 1)(Z - 1) / (Z - RR)$, and can be computed as

$$\text{Estimated Mortality Attributed to Spousal ETS} = 3379.65 \times \frac{(RR-1)(Z-1)}{Z - RR}$$

where 3379.65 is a proportionality constant such as that EPA's estimate of 860 is obtained when $RR = 1.19$ and $Z = 1.75$.

Based on the above formulas, the estimated mortality attributed to Background, Spousal, and Total (Background + Spousal) ETS exposure as a function of the assumed value of Z is shown in **Figures 1, 2, and 3** for values of RR equal to 1.19, 1.15, and 1.10, respectively.

As shown by Figures 1, 2, and 3, the estimated mortality is very sensitive to the assumed values of RR and Z , both of which are subject to considerable uncertainty. A Monte Carlo analysis was performed to help understand the distribution of possible values of the mortality estimates as a function of the uncertainty in RR and Z . For this analysis, the uncertainty in RR incorporates both the uncertainty in the smoker misclassification rate as well as the sampling distribution for the "true" Relative Risk. The uncertainty in the smoker misclassification rate is modeled as a compound distribution, consisting of a uniform distribution from 1% to 3% and a

EPA Estimate of Total (Spousal + Background) ETS-Attributable Lung Cancer Deaths
By Z-Factor

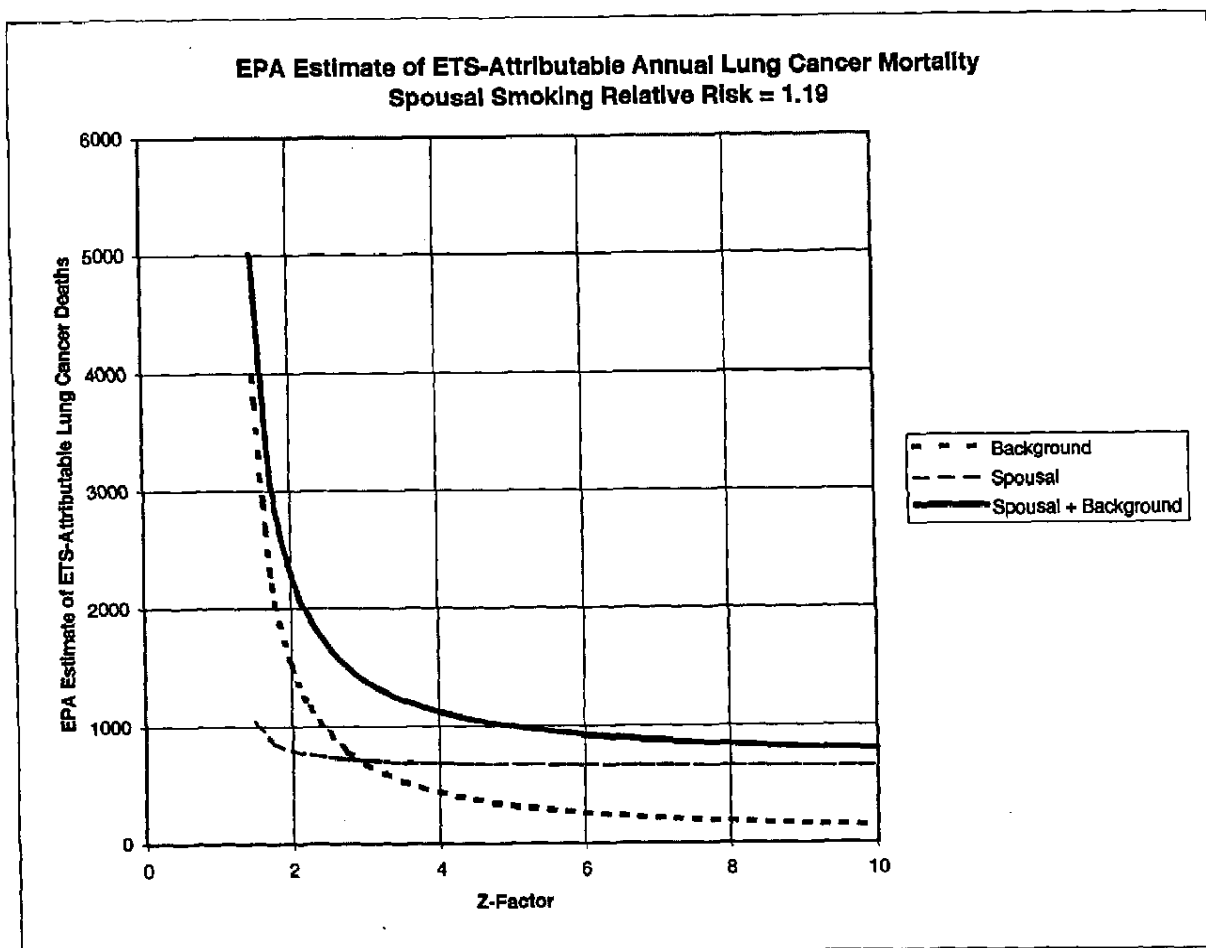


Figure 1.

EPA Estimate of Total (Spousal + Background) ETS-Attributable Lung Cancer Deaths
By Z-Factor

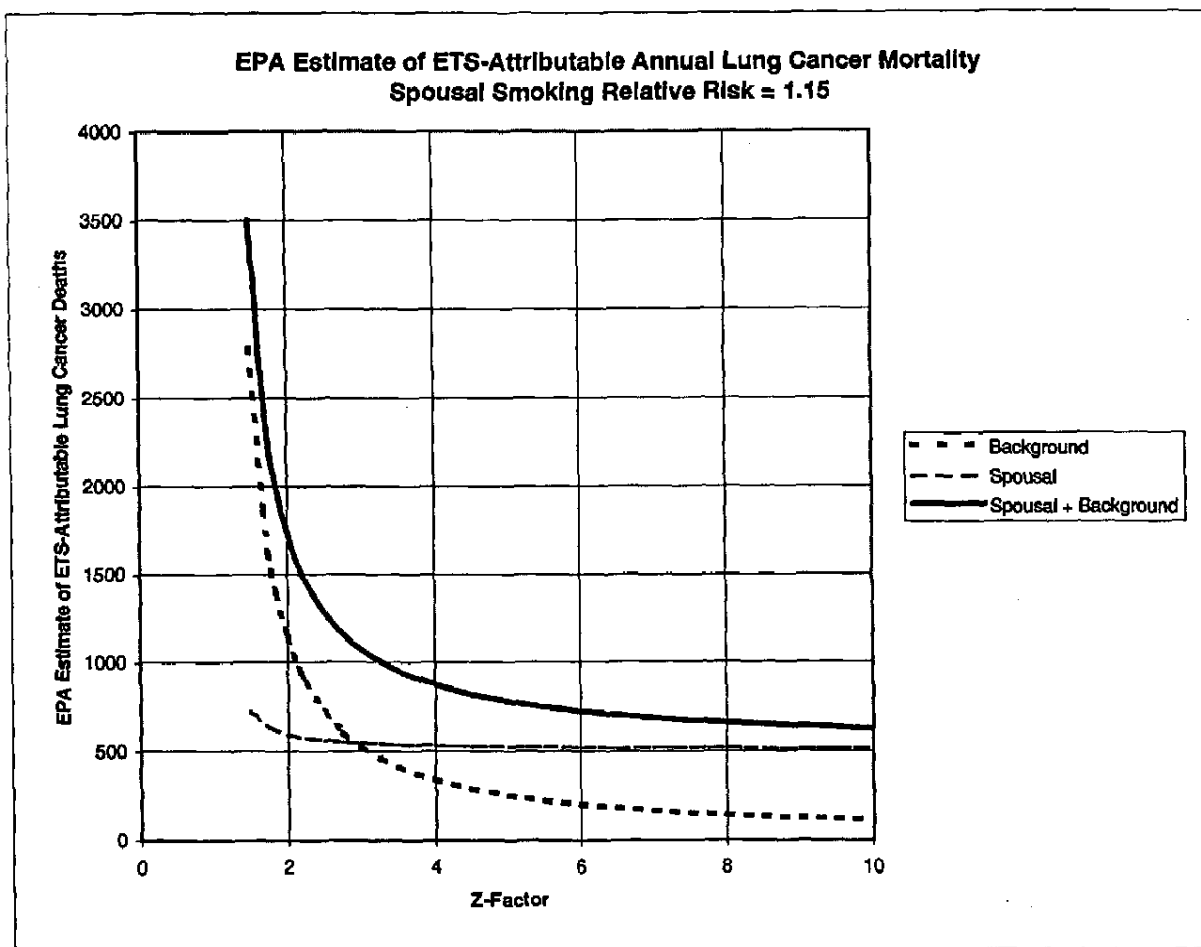


Figure 2.

EPA Estimate of Total (Spousal + Background) ETS-Attributable Lung Cancer Deaths
By Z-Factor

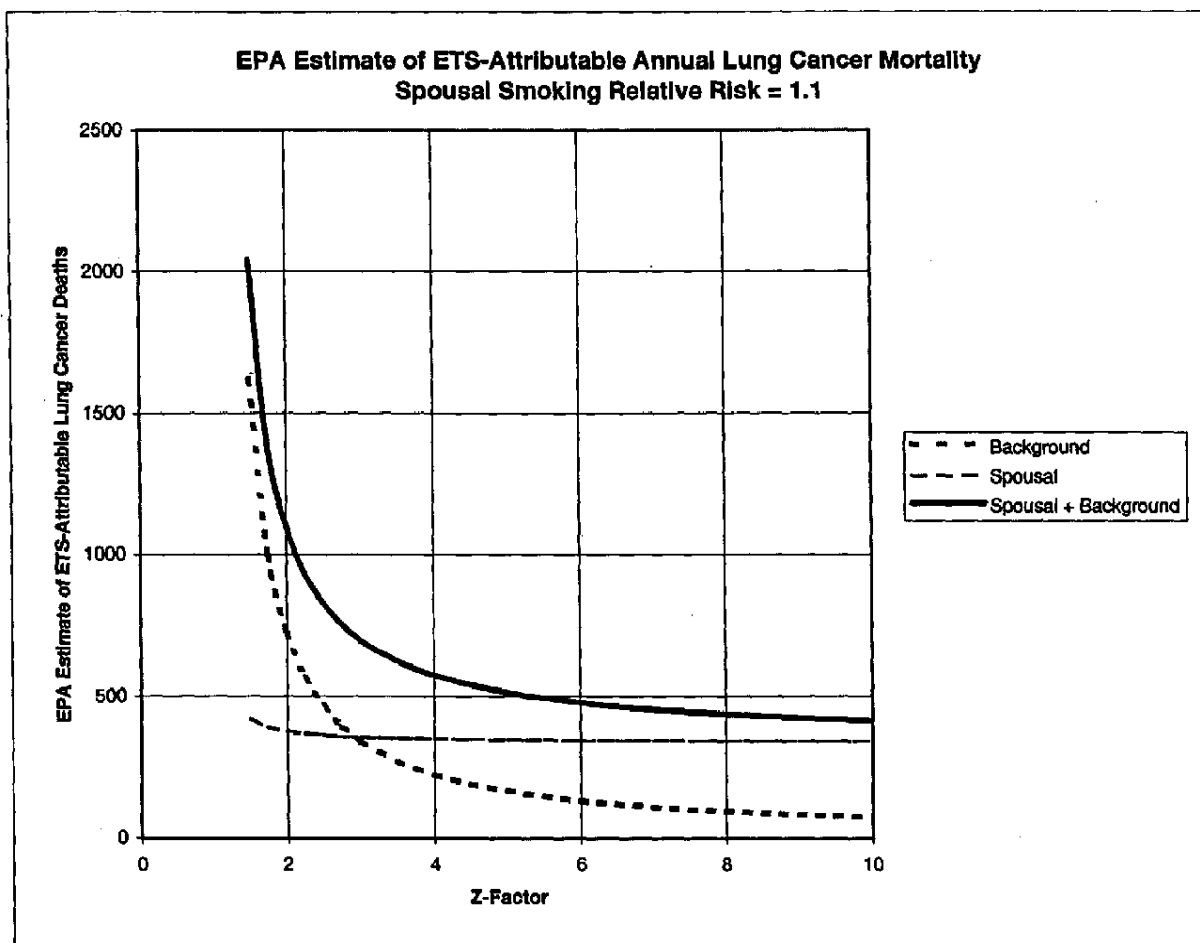
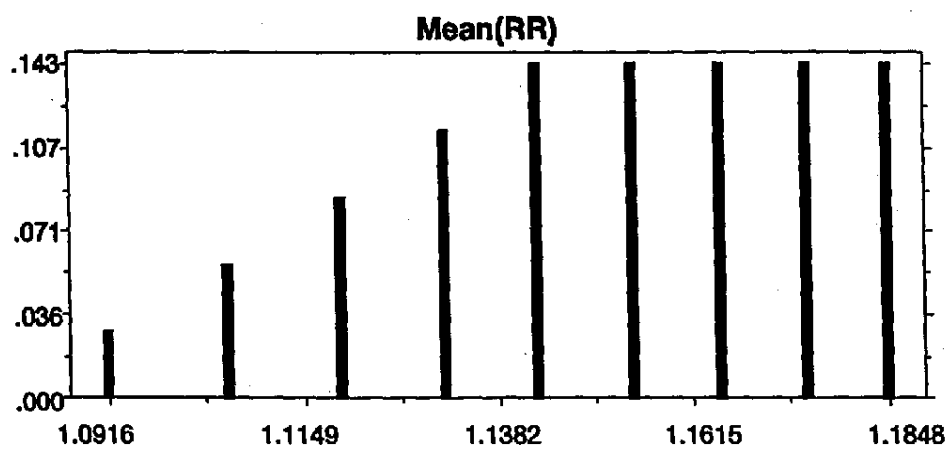


Figure 3.

Figure 4.



decreasing triangular distribution from 3% to 5%. Based on results by Ogden et al. (1997), the uncertainty in the smoker misclassification rate is simulated by using the distribution in **Figure 4** for the geometric mean of the Relative Risk distribution. The value of the "true" Relative Risk is estimated from a lognormal distribution with the randomly selected value of the geometric mean and a geometric standard deviation equal to 1.0825 (determined from the 90% confidence interval 1.04-1.35 for the "true" Relative Risk).

The uncertainty in the value of the Z-factor is represented by a compound distribution, consisting of a uniform distribution from 1.75 to 10, followed by a declining triangular distribution from 10 to 20. This distribution is shown in **Figure 5**.

Based on the preceding uncertainty assumptions for Relative Risk and Z-factor, the Monte Carlo analysis of estimated mortality was performed for 10,000 iterations using Crystal Ball® Version 4.0. Again, we reaffirm our strong view that the Relative Risk point estimate reported by U.S. EPA is scientifically unjustified and that our use of this value is solely illustrative. With this in mind, the resulting simulated distribution for mortality associated with Total (Background + Spousal) ETS exposure is shown in **Figure 6**. The mean and median of this distribution are 804 and 702 respectively, which are far below the EPA's estimate of 3,060. In fact, 3,060 is at the 98.7th percentile of this distribution.

In this simulation, uncertainty in the Relative Risk and Z-factor are represented by independent probability distributions. As stated in the EPA's report, however, the parameters RR

Figure 5.

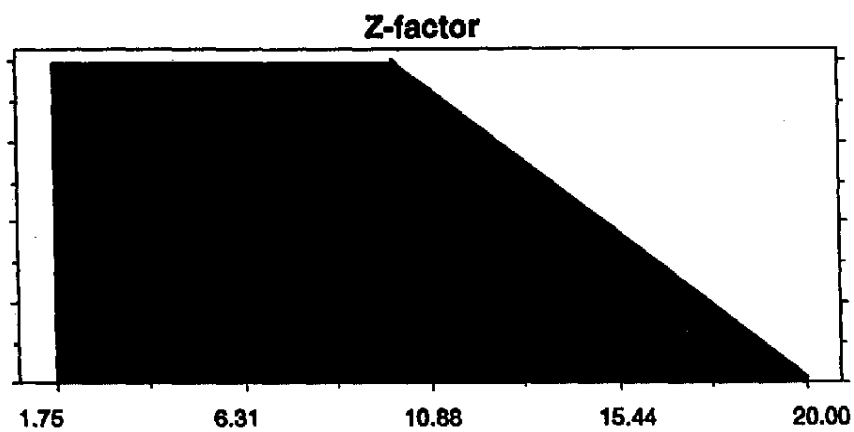
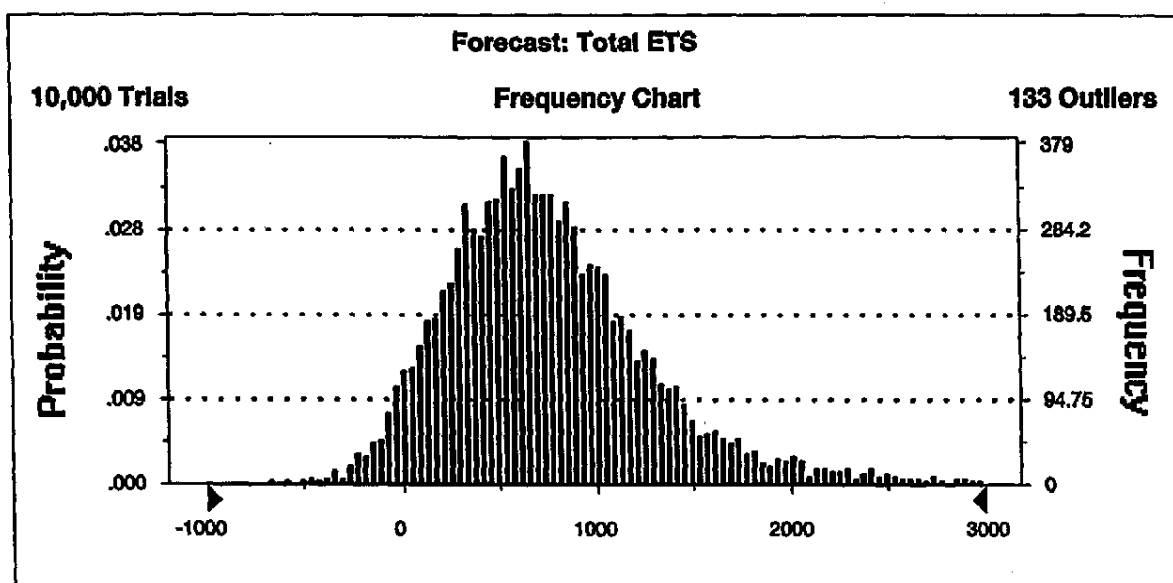


Figure 6.



and Z are not actually independent, but would be expected to covary in the same direction (to be positively correlated). For example, if the contributions of background to total ETS exposure decrease, Z would increase, and the observable relative risk from spousal exposure would tend to increase as well. Sensitivity analyses reveal that the effect of increasing correlation between RR and Z decreases the mean and standard deviation of the resulting simulated distribution of estimated mortality. Hence, estimates of mortality as high as 3,060 are even less likely than represented by the distribution in **Figure 6**.

References

Ogden, M.W., Morgan, W.T., Heavner, D.L., et al., National incidence of smoking and misclassification among the U.S. married female population, *Clin Epidemiol* 50: 253-263 (1997).

United States Environmental Protection Agency, *Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders*, Washington, D.C., Office of Research and Development, U.S. Environmental Protection Agency, EPA/600/6-90/006F (1992).